

## DERWENT PUBLICATIONS LTD.

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MITU 12.11.80

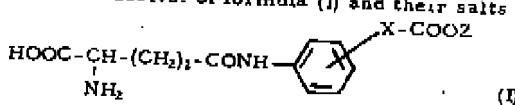
MITSUBISHI CHEM IND KK (NNSH)  
12.11.80-JP-159320 (+159319) (26.05.82) A61k-37/02\*EP-52-296  
C07c-  
103/52

Glutamine derivs. - useful as immuno-modulating agents with immunosuppressive and immunostimulating activities

D/S: E(AT BE CH DE FR GB IT LI NL SE)

Full Patentees: Mitsubishi Chem. Ind. Ltd. and Nippon Shinyaku Co. Ltd.

Glutamine derivs. of formula (I) and their salts are new.

(X is (CH<sub>2</sub>)<sub>n</sub>, vinylene or CR<sub>1</sub>R<sub>2</sub>;

n is 1-4;

R<sub>1</sub> and R<sub>2</sub> are each H or 1-4C alkyl, at least one being other than H; and

Z is H or 1-4C alkyl).

## USES

Cpd.s. (I) have immunomodulating activity, including immunosuppressive and immunostimulating activities, and

in 50 ml DMF was added and the mixt. stirred for 30 mins. with ice cooling, then for 8 hrs. at room temp. The solvent was evapd. and the residue purified to give an intermediate which was catalytically hydrogenated (Pd black) in aq. EtOH to give N-(4-ethoxycarbonylmethylphenyl)glutamate, m.pt. 179.8-180.5°C. (69pp1248).  
 (E) ISR.- J55026870 GB2034690 US4167449 J55036428  
 J55036454 3.Jnl.Ref

B(10-B2E, 12-A1, 12-A6, 12-D2, 12-G7) 4

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so are useful for treating autoimmune diseases, allergic conditions, cancer, bacterial infections, etc. Dose is 0.1-100 mg/kg parenterally daily or 0.001-1 g/kg orally daily.

## PREPARATION

Methods used include:

- (1) reaction of an amino-protected glutamic acid anhydride with a YO-CO-X subst. aniline (II) (Y is 1-4C alkyl), then the protecting gp. is eliminated. The protecting gp. for the NH<sub>2</sub> may include incorporation in a phthalimido gp.;
- (2) reaction of glutamic acid, having the α-COOH and α-NH<sub>2</sub> protected, with (II) in the presence of an activating agent; then protecting gps. are removed; and
- (3) reaction of a reactive deriv. at the γ-carboxyl of glutamic acid, having the α-COOH and α-NH<sub>2</sub> protected, with (II); then protecting gps. are removed.

## EXAMPLE

74.28 g N-benzyloxycarbonyl-L-glutamic acid α-benzyl ester and 28 ml NEt<sub>3</sub> were added to a mixt. of 250 ml THF and 250 ml DMF. The mixt. was stirred with ice-cooling and 26.4 ml ClCOO*i*Bu was added dropwise. The mixt. was stirred for 15 mins., then 35.84 g Et p-aminophenylacetate

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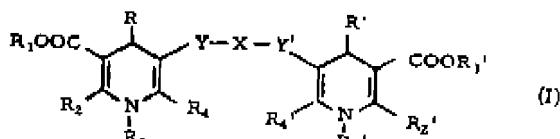
\*EP-52-300

13.11.80-DE-042769 (26.05.82) A61k-31/44 C07d-211/90 C07d-401/14 C07d-405/14 C07d-409/14 C07d-413/14

C3-Linked 4-aryl-1,4-dihydro-pyridine-3-carboxylic acid derivs. - with cardiovascular e.g. antihypertensive, vasodilator, cerebral or coronary activity

D/S: E(AT BE CH DE FR GB IT LI LU NL SE)

C3-linked 4-aryl-1,4-dihydro-pyridine-3-carboxylic acid derivs. of formula (I) and their salts are new.



(R and R' are aryl, thiienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, naphthyl, quinolyl, isoquinolyl, indolyl, benzimidazolyl, quinazolyl or quinoxalyl all opt. mono-, di- or trisubst. by phenyl, alkyl, alkenyl, alkoxy, alkenyloxy, alkylene, dioxyalkylene, halogen, mono- or

B(6-H, 7-D4, 12-C10, 12-E1, 12-F1, 12-F5, 12-G7) 5

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polyfluorocalkyl, mono- or polyfluoro-alkoxy, OH, NH<sub>2</sub>, alkylamino, NO<sub>2</sub>, CN, N<sub>3</sub>, COOH, carbaalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl and SO<sub>2</sub>-alkyl;R<sub>1</sub> and R<sub>1'</sub> are opt. branched or cyclic, opt. unsatd., hydrocarbon residues opt. interrupted by 1 or 2 O and opt. subst. by halogen or OH or by phenyl, phenoxy, phenylthio or phenylaluphonyl (all opt. subst. by halogen, CN, dialkylamino, alkoxy, alkyl, CF<sub>3</sub> or NO<sub>2</sub>);R<sub>2</sub>, R<sub>2'</sub>, R<sub>3</sub> and R<sub>4'</sub> are H or an opt. cyclic, opt. unsatd. hydrocarbon residue opt. subst. by halogen, OH, aryl or amino (opt. subst. by opt. subst., opt. cyclic, opt. unsatd. hydrocarbyl);R<sub>3</sub> and R<sub>3'</sub> are H, opt. subst. aryl or aralkyl, or opt. subst. alkyl the chain of which may be interrupted by 1 or 2 O;

Y and Y' are -CO-O-, CONH, CO-S, CO or SO<sub>2</sub>; X is a bridging gp. with  $\geq 1$  CH<sub>2</sub> and  $\geq 9$  adjacent CH<sub>2</sub>, the bridging gp. also contg. (in any order) 1-5 chain members selected from O, S, SO, SO<sub>2</sub>, CO, CS, NR<sub>5</sub>, C(R<sub>6</sub>)<sub>2</sub>, C(R<sub>6</sub>)=C(R<sub>6</sub>), C≡C, CH=CH, CH=N, arylene, heteroarylene, cycloalkylene, cycloalkenylene, piperazinylene, piperidylene, pyrrolidinylen and morpholinylene; R<sub>1</sub> is H, alkyl or aralkyl; and

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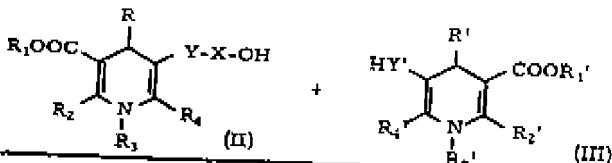
$R_4$  is H, aralkyl, aryl heteroaryl, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyoxy, alkylene, dioxalkylene, halogen, mono- or polyfluoroalkoxy, mono- or polyfluoroalkyl, OH, NH<sub>2</sub>, alkylamino, NO<sub>2</sub>, CN, N<sub>3</sub>, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or SO<sub>2</sub>-alkyl, the aryl, heteroaryl and alkyl residues opt. mono-, di- or tri-subst. by aryl, alkyl, alkoxy, aralkyl, dioxalkylene, halogen, mono- or polyfluoroalkyl, mono- or polyfluoroalkoxy, OH, NH<sub>2</sub>, alkylamino, NO<sub>2</sub>, CN, N<sub>3</sub>, COOH, carbalkoxy, carboxamido, sulphonamido, S-alkyl, SO-alkyl or SO<sub>2</sub>-alkyl).

USE

(I) have cardiovascular activity and can be used as antihypertensives, vasodilators, cerebral agents and coronary agents. They have a partic. prolonged duration of action.

PREPARATION

E.g.



\*The reaction is in an inert organic solvent at 0-180°C in the presence of dehydrating agents using equiv. amts. of (II) and (III).

EXAMPLE

2,6-dimethyl-5-(4-hydroxybutoxy-carbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid ethyl ester (25 mmol), DCC (25 mmol) and 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid (25 mmol) in anhydrous DMF (50 ml) are heated 4 hrs. at 100°C with 4-dimethylaminopyridine (0.2 g), then worked up to give 2,6-dimethyl-5-ethoxycarbonyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid 2,6-dimethyl-5-methoxycarbonyl-4-(2-chlorophenyl)-1,4-dihydropyridine-3-carboxylic acid 1,4-butanediyl ester, as an amorphous foam in 25% yield. (G) ISR: DE2847236 DE1795791 DE2117571

EP--52300

44121 E/22 B03 STER 19.11.80  
STERLING DRUG INC \*EP--52-311  
24.06.81-US-297759 (+208259) (26.05.82) C07d-211/26  
N-Benzoyl-phenyl-alkyl-piperidine derivs. and analogues - useful as bronchodilators, anti-asthmatics, anticholinergics

D/S: E(BE CH DE FR GB IF LI LU NL SE).

N(Benzoylphenylalkyl)piperidine derivs. and analogues of formula (I) and their acid-addn. salts are new.

Ph-CX

(R is H or 1-6C alkyl;  
m is 0 or 1;  
n is 0 or 1;  
B is 1-piperidinyl, 4-morpholinyl, NH<sub>2</sub>, di-(1-6C)alkylamino, 1-6C alkanoylamino, N-(1-6C)alkyl-N-(1-6C)alkanoylamino, cycloalkanecarbonylamino, or PhCONH opt. ring subst. by 1-6C alkyl, halogen or 1-6C alkoxy;  
CX is CO or CH(OH);

B(7-D5, 12-D2, 12-E4, 12-G1, 12-K2) 5

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PhCX is attached to the 3- or 4-posn. when m is 1 or only to the 3-posn. when m is 0; provided that when m is 0, n is 1, R is alkyl and N=B is 1-piperidinyl or 4-morpholinyl).

USES

(I) are bronchodilators, antiasthmatics, antiallergics, anticholinergics and prostaglandin synthetase inhibitors.

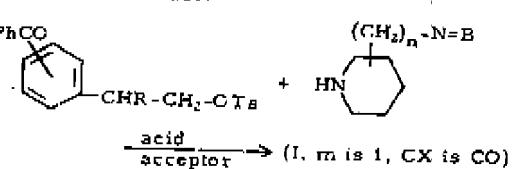
SPECIFICALLY CLAIMED

8 Cpd. (I), including 1-(2-(3-benzoylphenyl)propyl)-4-acetylaminopiperidine HCl and the corresp. 4-benzoyl cpd.

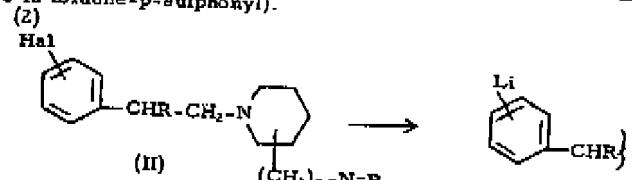
PREPARATION

Methods used include:

(1)



EP--52311

T<sub>2</sub> is toluene-p-sulphonyl.

(1) Benzonitrile → (I; m is 1, CX is CO)  
(2) Hydrolysis

(3) When m is 1, redn. of a corresp. ketone, i.e. with a CHR-CO- bridge, with LiAlH<sub>4</sub> gives the prod. When CX is CO, it may be protected by ketalisation etc.

EXAMPLE

10.17g  $\alpha$ -(3-benzoylphenyl)propionic acid in 25 ml benzene was treated with 9.52g SOCl<sub>2</sub> and refluxed for 3.25 hrs. The mixt. was evapd. and the residual oil in 25 ml CH<sub>2</sub>Cl<sub>2</sub> was added to 4.86g NEt<sub>3</sub> and 7.29g 4-(1-piperidinylmethyl)piperidine over 15-20 mins. at about 5°C. The mixt. was stirred for 3 hrs., washed with water, aq. NaHCO<sub>3</sub> and aq. NaCl, filtered and evapd. to give 1-( $\alpha$ -(3-benzoylphenyl)-

propionyl)-4-(1-piperidinylmethyl)piperidine as an oil. It formed a HCl salt, m.pt. 211-212°C. (42pp1248). (E) ISR: GB1250719 US3816434 GB1508391 FR1549342 US4216326.

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